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UNIVERSITY OF TORONTO MEDICAL JOURNAL

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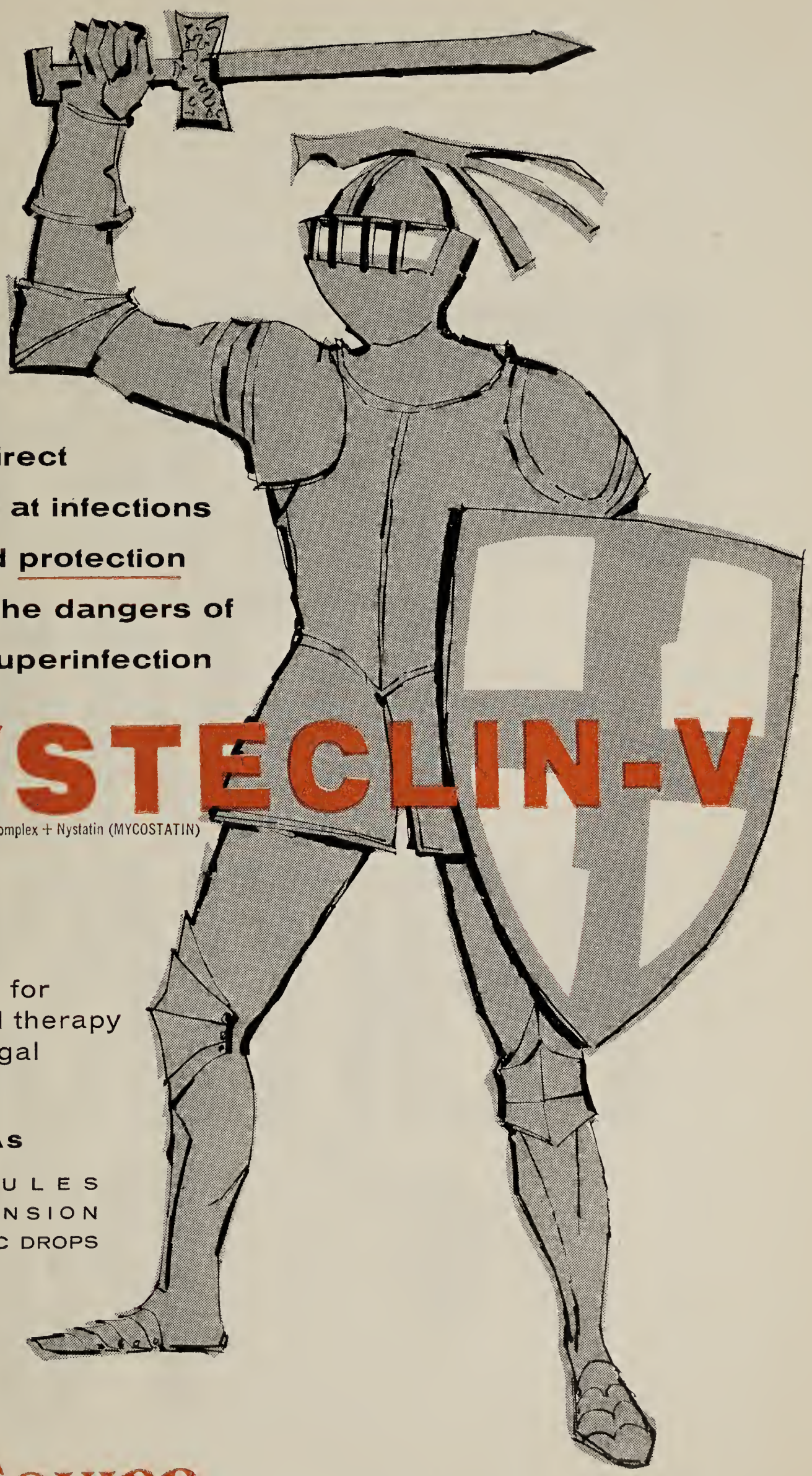

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EDITORIAL

Volume XXXVII of the University of Toronto Medical Journal may be a crucial one for this the oldest undergraduate medical journal in Canada. Over the last few years the Medical Journal has been taken for granted by the student body. Its appearance every month is just something that happens and no one gives any thought as to how and why it happens. Few are aware that the Journal constitutes the Medical Society's second largest expenditure. We wonder what factors justify the existence of the Journal and what factors threaten its existence.

On the positive side of the balance are the following. Fulfilling its purpose as a medium for student expression it has come to occupy a necessary place in the training of the undergraduate: it fosters academic medical knowledge and writing ability to help to produce a literate doctor. It prepares us as students for the time when we will want to communicate with our colleagues through the medium of the graduate medical journals. It publicizes the excellence of our medical school and our research centres (Volume XXXVI No. 4). It provides new perspectives on old problems and it summarizes ideas on current problems.

On the negative side of the balance are two things, a large debt and apathy. For as long as we can remember the Medical Journal has been carrying this debt on its books. The amount has fluctuated with varying amounts of advertising, with increased subscription rates and increased advertising rates, with decreased circulation and with timely handouts from the Medical Society. The fact remains that we are still saddled with the debt and costs continue to rise so that if we do not shake off the second factor—apathy—we will be in serious trouble. Contrary to what one would think apathy is no stranger to the Medical Journal. One editor in 1927 concluded an editorial on lack of interest and contributions by observing that apathy has the advantage of providing the editor with something to write about each year. Nor is this affliction peculiar to Toronto for our associates across Canada and in England often complain of it. It is endemic in all aspects of our Journal; a glance at the decreasing size of the masthead over the years is as good an indication of dwindling student interest as anything. It used to be a privilege to join the Journal staff; now the editor must make personal pleas for volunteers to work on the Journal. The maximum benefit from the Journal cannot be obtained unless the maximum number of people are concerned with its production. Advertising has managed to hold its own over the years and is in surprisingly good shape considering the amount of work that has been done in this department. Circulation has fallen off through alumni disinterest and through editorial neglect of maintaining the graduate appeal of the Journal.

We have explained our problems frankly without the customary euphemisms, without glossing over the true picture, trying not to lull you into a false sense of security. The situation is not a grave one nor is it irremediable but we must be aware that it exists in order that we may do something about it.

This year we hope to present articles of wide interest, including a special report on some of the research work being done in Torono and a few articles written by the preclinical years. We plan to revive such features as On Inspection (for at least two issues) and News and Notes. We hope to increase the size of the Journal staff, particularly with junior members to maintain a continuity throughout the years. We would like to increase the advertising and the circulation but to make promises would be foolish. With the aid of the Medical Alumni Association we hope to increase the graduate appeal and hence the circulation of the Journal. With some hard work and enthusiasm we hope to swing the balance definitely to the positive side but in the final analysis it will be up to you to justify the existence of the Medical Journal. We need your support.

TO THE FRESHMAN

With this first issue of Volume 37 of the University of Toronto Medical Journal we would like to take the opportunity to extend a warm welcome to all the new students who have enrolled in the first premedical year. You have enrolled at a medical school which is rated among the best and which has produced many distinguished and well known graduates. You are embarking on what should be the most enjoyable and most inspiring six years of your lives and we congratulate you and wish you the best of luck in your endeavours.

A special welcome is also extended to the new students in the first medical year who have joined us from other fields of study and other Universities. In the past the advanced standing students have always had a great deal to contribute to medical student life at Toronto with new ideas and new personalities, and we look forward to meeting you and having you as fellow students.

Upon enrolling in the Faculty of Medicine each student automatically becomes a member of the Medical Society, an organization designed to serve the welfare and general interests of the medical undergraduate body. The Society is directed by a governing body known as the Medical Society Assembly which is responsible for organizing the numerous activities and projects of the Society, of which this journal is one example. With such things as Medical Athletics, Daffydil, the Debating Society, the Music Club, and many others we feel that we are providing an opportunity for each student to participate in some extra-curricular activity in accordance with his own individual interests. We hope that you will take advantage of this opportunity, and join in that unique spirit which has become traditional among Medsmen at Toronto.

Bob Lee
President, Medical Society

IN MEMORIAM

Dr. W. E. Gallie, the Father of Canadian Surgery, passed away on September 25, 1959. He died in his sleep in Princess Margaret Hospital where he was being treated for cancer, after having been ill only a short time.

Dr. Gallie graduated from the University of Toronto Faculty of Medicine in 1903, the youngest member in his class. He went on to achieve world-wide fame and recognition for his outstanding contributions to medicine. He held the post of head surgeon at the Hospital for Sick Children and later the Surgeon-in-chief at the Toronto General Hospital. He received the Gold Medal of the Royal Society of Edinburgh, and was created a Fellow of the Royal Society together with the Duke of Edinburgh. Dr. Gallie was Professor of Surgery at the University of Toronto from 1929 to 1947 and also Dean of the Faculty of Medicine from 1936 to 1947. He remained on the staff of the Faculty as Professor Emeritus of Surgery until his death.

William Edward Gallie was surrounded at his funeral, as he had been in life, by his colleagues, family, and friends. The funeral service, held on September 29 in Convocation Hall, was conducted by Rev. Dr. D. R. G. Owen, provost of Trinity College, whose family had been long-time friends of the Gallies. During the service, medical students across the campus were studying textbooks written by Dr. Gallie, and in the hospitals, operations were going on using methods Dr. Gallie had pioneered and for which he had received world recognition. It is with great sorrow that we mourn the passing of this outstanding Canadian.

SMOKING—WHY QUIT?

L. E. DORFMAN, 6T0

OVER eighty million North Americans smoke and enjoy it. A realistic survey of this population reveals that, after air, food and water, most adults concern themselves with a fourth item of consumption: tobacco. For these millions, smoking in one form or another may be classed as a basic appetite, and a habit and pleasure not to be lightly swept aside.

Nevertheless, smoking is being spoiled for the public these days. Scare headlines reveal statistics which show tobacco leads to heart disease and cancer. Non-smoking friends and relatives, especially the reformed variety, tell you how much healthier and wealthier you'd be if you gave up the depraved habit. Pamphlets, tracts, books and magazine articles urge one to break the bonds of slavery or suffer ghastly consequences outlined in meticulous detail.

There is no doubt that the lay press, and the medical profession from which it ultimately derives its information, are saying some very frightening things about smoking. The controversy over tobacco—to smoke or not to smoke—has become a hotly debated issue, charged with such emotional slogans as "cancer by the carton", and "smoke less—live longer". Cigarettes have acquired such sinister nicknames as "coffin nails", "weeds", "gaspers" and "little white slavers". Just what is all the shouting about? Is tobacco smoke really harmful? Does smoking cause or influence organic disease? Is smoking a killer? Is the smart smoker the non-smoker?

Let's see. . . .

THE CHEMISTRY OF TOBACCO SMOKE

Just what is there in tobacco smoke which is harmful? Better to ask the question in reverse, because the only components not proven harmful are carbon dioxide and water vapour. About two-thirds of the non-gaseous content of smoke have yet to be characterized, but the *known* substances read like a Borgia recipe. The more familiar include:

formaldehyde; acetaldehyde; acrolein; acetone; formic, acetic, benzoic and phenolic acids; methyl alcohol; ethylene glycol; phenol; cresol; alkaloids; and toxic amines (including the well-known nicotine); methane; acetylene; anthracene; pyrene; 3, 4-benzpyrene (the mouse-skin carcinogen); resins; tars (a fine, wide field); ammonia, carbon monoxide, hydrogen cyanide; hydrogen sulphide; aluminum, arsenic, chromium, copper, lead, manganese, nickel and iron.

Obviously none of the above are present in smoke in amounts sufficient to do one in, else the human race would have long since vanished; but tobacco smoke is far from innocuous. An industrial worker labouring in such fumes would give the Division of Industrial Hygiene apoplexy—he would be breathing 50 times the maximum allowable concentration of arsenic, 40 times that of hydrogen cyanide, 10 times that of hydrogen sulphide, 8 times that of carbon monoxide and 1.5 times that of ammonia. The amounts of non-specific mucous membrane irritants would preclude entering the atmosphere without goggles and a respirator. Clearly the happy smoker is protected from rather violent consequences because he drags on his cigarette intermittently, and dilutes his mouthful of smoke with a large volume of air as he inhales.

THE PHYSIO-PHARMACOLOGY OF SMOKING

As tobacco burns, over two hundred chemicals appear, interact, combine and vanish, for the most part, down the

smoker's throat. Despite the solvent and mechanical trapping actions of respiratory mucus, ninety per cent of these substances reach the alveoli, (a percentage, incidently, considerably higher than most tobaccophiles would care to consider). It is not in the least surprising, then, that smoke can exert rather startling systemic and local effects.

Nicotine is the most familiar component of tobacco smoke, and is responsible for its acute systemic toxicity. The drug has a bad record. One drop on a cat's tongue stiffens it almost as quickly as cyanide; the total content of three cigarettes injected into a man does likewise. However, since humans take nicotine neither as a beverage nor as a road to Greater Glory, only its effects as absorbed by the respiratory route need to be considered.

In doses acquired by consuming one cigarette (about 3 mgm.), nicotine exerts four specific pharmacologic effects: it stimulates the autonomic ganglia of both sympathetic and parasympathetic types, it increases the activity of most medullary centres, it excites the peripheral chemoreceptors, and causes the supra-optic nuclei to secrete vasopressin. The results, although similar in chronic smokers, are best observed in the callow youth sneaking his first smoke behind the barn.

On his circulatory system, the action of nicotine is primarily adrenergic, due to widespread stimulation of sympathetic ganglia (parasympathetic ganglia are much less affected), and reinforced by release of epinephrine from the adrenal medulla. His heart rate increases, up to twenty beats per minute; his blood pressure skyrockets to an average level 38/30 mm. higher than before; peripheral vasospasm leads to cold sweaty palms, and blood flow to the extremities falls by as much as 25%. A wave of nausea sweeps him as the vomiting centre is stimulated, he feels faint as his cerebral blood vessels constrict, and hot and cold flushes assail him as his pressor reflexes madly adjust. Carotid and aortic body reflexes lead to hyperventilation, and reinforce the tachycardia and generalized vasospastic response. Coronary blood flow, at first increased with rising blood pressure, falls as posterior pituitary hormone is released and causes secondary coronary vasoconstriction as well as a mild antidiuresis. Blood sugar rises as much as 65% as glycogenolysis proceeds in response to adrenalin. Even after the butt is crushed, it takes nearly half an hour for the smoker's physiology to return to a basal state.

The effects of nicotine on the gastrointestinal tract are less characteristic and subject to more individual variation. In general, it augments colonic function (the first morning cigarette often producing a pressing urge to defaecate), causes a rise in gastric acidity, and decreases gastric motility with a consequent easing of hunger pangs.

Irritants sufficiently strong to produce edema, erythema, and permeability changes in the mucous membranes are present in abundance in tobacco smoke; they include organic and inorganic acids, ketones, alcohols, phenols and aldehydes. The two-pack-a-day man knows the feeling of a mouth like a fur-lined sewer, the tingling tongue, the clogged nose, and butterflies in the chest, perhaps relieved by hawking phlegm out of his throat morning and night.

Tars collected from tobacco smoke have, interestingly enough, no irritant effects in themselves—they are as inert as the floor waxes which they closely resemble. The harmful effects of these substances on the bronchial mucosa is apparently due to their ability to cling to the respiratory passages and bind water soluble irritants listed above. The role of tars in the pathogenesis of carcinoma is discussed below.

Carbon monoxide absorbed from smoke forms carboxyhaemoglobin in concentrations up to 10%, depending on tobacco consumption. It has no deleterious effects, except to render the heavy smoker mildly hypoxic.

Arsenic, cyanide, hydrogen sulphide and other chemicals appear in amounts too small to exert notable effects, as long as inhalation is intermittent.

SMOKING AND HEALTH

Tobacco has been blamed for just about every human ill imaginable—physiological, psychological, sociological, pathological, political, economic and moral. At the same time, it has been hailed as a panacea for ills ranging from baldness to beri-beri. Until very recently, however, our knowledge concerning smoking has been in inverse proportion to a veritable mountain of superstitions, myths, and pseudo-scientific garbage. The smoker of today need no longer worry that tobacco gains its flavour by being stored in outhouses, that the whiteness of cigarette paper is due to its being bleached with arsenic and white lead, that lepers are the chief producers of the paper, and that some of the tobacco mixture is compounded from butts gleaned from the horse travelled gutters. He still, however, has his troubles.

The effect of smoking on the circulatory system (*supra*) has implications well worth considering. There is no evidence that the use of tobacco actually *causes* cardiovascular disease (thromboangiitis obliterans excepted), but there is much reason to think that it aggravates such pathology once established. Nicotine will increase the load on a damaged heart and drive up the blood pressure of the hypertensive. Deterioration of the ECG after smoking occurs so frequently in those with coronary artery disease that it has been suggested this be used to aid diagnosis of the incipient condition. Anginal attacks are sometimes precipitated or aggravated by smoking. Excessive use of tobacco is one factor in the etiology of extrasystoles and paroxysmal atrial tachycardia; thus, in the period immediately following a myocardial infarction it is wise to discontinue smoking lest it induce arrhythmias in the hyperirritable heart muscle.

Smoking also hastens the progress of peripheral vascular disease. Non-smoking diabetics have less than half the incidence of arteriosclerosis of their smoking counterparts. Raynaud's phenomenon may be precipitated by smoking one or two cigarettes in persons subject to it; those suffering from the syndrome should be advised against tobacco. The common practice of giving injured persons a smoke may, in the presence of arterial damage, cause irreversible segmental spasm and vasoconstriction of the vessel. The fact that thromboangiitis obliterans is caused by smoking, and that the disease never becomes quiescent as long as the patient smokes even occasionally, is best illustrated as follows:

> A patient discovered to have thromboangiitis obliterans in 1940 ceased to use tobacco on medical advice, and his disease remained quiescent until 1949. Impressed by advertisements extolling the virtues of "de-nicotinized' cigarettes, he again took up the habit, and within 6 months gangrene of three toes had developed. On abstinence from smoking (and other treatment) the disease again subsided. In 1954, believing claims made for filter-tips he again began to smoke, and was shortly seen with pre-gangrenous involvement of two toes.

So much for the evils of modern advertising.

Needless to say, smoking does not exactly benefit the gastro-intestinal tract either. By increasing gastric acidity it helps produce a situation in which ulcers thrive, and is one factor responsible for failure to improve on ulcer therapy. It may also result in a variety of functional disturbances—heartburn, eructation, anorexia, nausea, flatulence, epigastric distress, and even severe diarrhoea or constipation—all of which are relieved on ceasing to use tobacco.

The individual who really overdoes his smoking risks a rare and incapacitating disease known as tobacco amblyopia, a toxic neuritis of the optic nerve. Reversible at first, continued use of tobacco leads to papillomacular atrophy in the retina and partial blindness.

The minor maladies associated with

the tobacco habit deserve at least passing mention. The smoker usually manages to burn himself (or his aquaintances) once in a while. His halitosis can be quite overpowering at times, and the stains on his teeth may spoil his Pepsodent smile, but they will at least match the yellow cast between his second and third fingers.

It is the effect of smoke on the respiratory tract, however, which deserves our closest attention. As a cause of chronic rhinitis, sinusitis, pharyngitis, and laryngitis it is second to none: the heavy head, plugged nose and chronic cough of the tobacco habitué give adequate proof of this fact. Moving down the respiratory tree, smoking is the commonest factor involved in the pathogenesis of chronic bronchitis and emphysema, with its grisly sequelae. Veterans' hospitals have more than a fair share of these respiratory cripples, probably because of the relative cheapness of tax-free tobacco available to the armed forces. But every medical ward has its dyspnoeic old smoker who, with clubbed fingers lifts his cigarette to cyanosed lips, strains to draw the fumes into his barrel chest, and relaxes as failing heart drives the nicotine through his edematous system. It is noted that about one-third of the population is allergic to tobacco extract according to intradermal tests for atopy—the effect of this factor on the respiratory epithelium is still being investigated, but speculation offers some interesting possibilities.

Is smoking "a" cause of bronchogenic carcinoma? If you believe in statistics, the answer is yes. If you don't believe in them you have plenty of company—80 million smokers in North America alone, some of them leaders in the medical profession. The facts are these:

1. A fourfold increase in lung cancer cases in recent decades has been accompanied by a sharp increase in cigarette smoking in the same period.
2. Lung cancer is four times commoner in men than women; men have smoked longer and more feverishly than women.
3. The great rise in lung cancer has been of the epidermoid bronchogenic variety; this type of carcinoma arises primarily in sites of chronic irritation; tobacco smoke is irritating.
4. Tobacco is a proven animal carcinogen.
5. No other explanation has been offered for the above relationships, other than smoking cigarettes promotes carcinogenesis. Decriers of this theory do not deny the interpretation of the above findings, but suggest that the statistical survey techniques leave something to be desired.

Perhaps, to plagiarize a popular cigarette advertisement, "every man should think for himself".

WHY DO PEOPLE SMOKE?

The good that can be said for the tobacco habit is pitifully small. It is suspected of discouraging tooth decay, but since smoke is not too kind to the gums, one may preserve the teeth at the expense of failing to keep them in the head. It may be good for constipation, and it may keep cannibals from serving you table d'hôte. White man's meat, say reliable native sources, is disgustingly impregnated with tobacco smoke. There is proof aplenty, however, that the less you smoke the longer you live, and no one likes to think that every cigarette is pushing him one closer to becoming a statistic. Why, then, do people smoke?

They smoke because the values they derive from the habit are greater than its drawbacks. In our manic-depressive, extrovert world smoking helps us relax, eases our tensions, and provides pleasure in a life where worries are many and tranquillizers few. Even when faced with the possibility of leaving this earth a few years early, the vast majority of smokers prefer to play the odds rather than forsake the habit. After all, worries tweak more ulcers than smoking ever could. But the sheer perversity of the tobacconophile is best expressed in these few lines by Graham Menninger:

"Tobacco is a dirty weed: I like it.
It satisfies no normal need: I like it.
It makes you thin, it makes you lean,
It takes the hair right off your bean.
It's the worst darn stuff
you've ever seen.
I like it."

THE MALIGNANT CARCINOID SYNDROME

MARTIN BARKIN, 6T0

This man was addicted to moanin',
Confusion edema and groanin',
Intestinal rushes,
Great tri-colored blushes,
And died of too much Serotonin.

ABOVE, in limerick form is described a syndrome which at one time fell into the "exceedingly rare" category of diseases. In the last four years interest in this syndrome has led to extensive research, the results of which embrace not only surgery, but internal medicine, pharmacology, psychiatry, endocrinology, and a host of sub-specialties.

The carcinoid is a tumour whose origin is believed to be the chromaffin cells of the intestinal mucosa, known as Kulchitsky or K-cells. It has a combined surgical and autopsy incidence of 0.1%. Of this, about two-thirds are found in the appendix of young adults where it is usually an incidental finding. Of the remaining one-third, 70% are found in the small intestine of middle-aged people. Other sites of origin which are rare include teratomas of the ovary and testis and some dubious cases arising in the bronchial lining.

In the gross the appearance in the appendix is that of a firm, rubbery, pale yellow tumour ranging from pinhead size to ten centimetres or more in diameter and displacing all of the structures in its area.

Microscopically, the tumour consists of small irregular cords of cells, supported by a scant stroma. These cells show poorly defined cytoplasm and have small dark staining nuclei. The cytoplasm is often vacuolated and has staining properties similar to the cells of the adrenal cortex. Encapsulation is poor, and invasion into the mucosa, submucosa, muscle and serosa often occurs.

The tumour is extremely slow in its growth and histologically appears benign, yet metastases do occur to regional lymph nodes and by peri-venous lymphatics and perhaps by the portal vein to the liver and from there to lung, hence the name carcinoid. About 75% of tumours originating in the small bowel metastasize, 20% of those arising in the stomach, 50% of those arising in the large bowel, and 1% of those arising in the appendix. The low incidence of metastases from carcinoid of the appendix is likely due to the frequency of surgical appendectomy.

The greatest interest in this tumour centers around its biochemical function. The carcinoid removes tryptophan from the circulation and synthesizes serotonin which is carried to the liver and metabolized to 5-hydroxy-indole-acetic acid (5-HIAA), a harmless metabolite. All of the bizarre symptoms of carcinoid are probably attributable to serotonin (see diagram).

The syndrome consists of the following clinical features;

1. Dependent edema, frequent watery stools, borborygmi, and abdominal pain.

2. Generalized widening of the small vessels of the skin with, in some cases, telangiectasia.

3. Peculiar, patchy flushing of the skin, combined with pilomotor symptoms, plethoric coloration and total or partial cyanosis in the absence of polycythemia.

4. Valvulitis usually limited to the right side of the heart and usually appearing as pulmonary stenosis.

5. Attacks of an atypical type of asthma.

6. Pellagra, in some cases due to the large amounts of tryptophan metabolized by the tumour.

7. The usual symptoms of neoplasia,

including a mass, cachexia, anorexia, enlarged irregular liver.

In experimental animals, in tissue extracts and in man, serotonin has been shown to have a great many physiological and pharmacological activities. It first came to the attention of physiologists as a peculiar agent found in high concentrations in platelets and whose liberation by these tiny agents of clotting caused retraction of the clot and its first name was therefore retractozyme. Other actions which have been demonstrated include;

1. A smooth muscle stimulant acting on bronchi, arteries, veins, and on the intestine. In the latter it stimulates both tonus and motility. It has been postulated that one of the physiological functions of serotonin is as a humoral agent regulating bowel activity.

2. It is an antidiuretic.

3. It is capable of producing marked central nervous system disturbances. It is found in great concentrations in the mesencephalon and diencephalon and in lesser concentrations in the cerebellum and neocortex. Its direct pharmacological antagonist is LSD (lysergic acid) a known schizophrenogenic drug.

4. On blood vessels it acts as a vasoconstrictor of both artery and vein but acts as a dilator of the intermediary vessels.

It appears quite definitely that most, if not all, of the symptoms which comprise the Malignant Carcinoid Syndrome are directly attributable to serotonin. However, as we expressed before, serotonin is metabolized in the liver to a harmless product, 5-HIAA. It follows then that these symptoms will not occur when the tumour lies in the intestinal tract and is therefore drained by the portal vein. However, should metastases appear in the liver, or should the tumour occur in a teratoma of the testis or ovary, serotonin will reach the inferior vena cava without first passing through the liver. It has also been noted that serotonin is partially deactivated in the lung. For this reason cardiac lesions are predominantly right-sided. It follows therefore, that when the symptoms of carcinoid appear in most cases they represent metastatic disease.

The diagnosis of carcinoid, except in the appendix where it produces early symptoms, is extremely difficult before metastasis occurs. However, once the tumour releases its serotonin to the systemic circulation, the diagnosis is suggested by the clinical picture, and verified by the biochemical findings. The ideal over-all screening test is done on urine, tests not for serotonin, but for its metabolic product 5-HIAA. Normal levels are from two to nine milligrams daily. Pathognomonic levels range from twenty-five to over one thousand milligrams a day. Non-specific increases follow the ingestion of bananas and interference with the accurate analysis of the sample is obtained with certain drugs, especially those in the promazine-chlorpromazine group.

The prognosis is excellent as far as mortality is concerned even in untreated cases. The tumour grows very slowly and survivals of 15 to 20 years are not uncommon.

Treatment of metastatic carcinoid is poor. Surgery is limited to those cases where the tumour is producing a mechanical effect that is giving rise to severe symptoms. In some cases where the tumour occurs in a teratoma surgery is curative. In a few cases where the symptoms of the Carcinoid Syndrome have been extremely severe, alleviation has occured following the removal of the primary. Anti-neoplastic drugs and radiation are useless here. The uses of tryptophan labelled with radioactive elements is still in the experimental stages. The flushing and diarrhoea are usually controlled with large doses of chlorpromazine.

SUMMARY

Carcinoid is a slow growing tumour usually found in the intestine. It is histologically benign but does metastasize. It produces large amounts of serotonin.

This latter substance produces a great many effects which ultimately give rise to the Carcinoid Syndrome. Serotonin is detoxified by the liver. The prognosis is usually good. The symptoms, however, can at times be very distressing.

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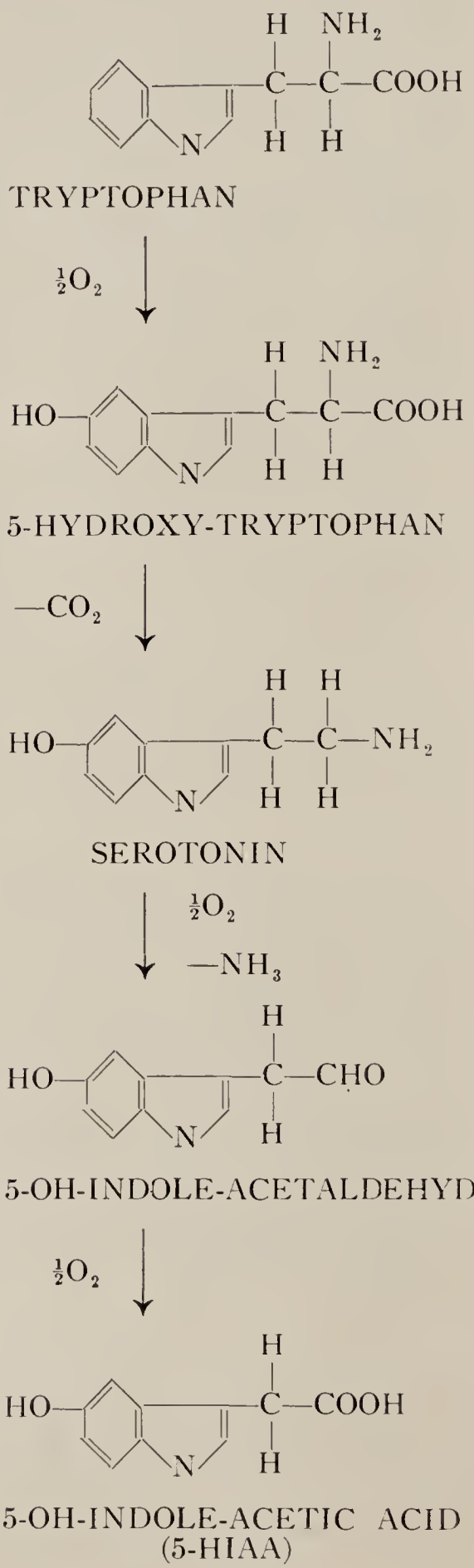

SOME CALCULATED RISKS IN BLOOD TRANSFUSION

WALTER SPITZER, 6T2

THE discovery of the human blood groups by Landsteiner (1901), and information gained by numerous other workers over the past fifty years has made blood transfusion a practicable and relatively safe procedure. Advances in this field however may cause some physicians, who are anxious to relieve their patients from such conditions as shock and anaemia, to overlook the disadvantages of transfusion.

It is important to be aware of the fact that blood transfusion is not a completely successful therapy in every patient. Moreover, apart from being ineffectual, in many patients blood transfusion is actually harmful. This is true in more cases than the attending doctors may appreciate because the ill effects may not appear for a considerable time after the transfusion is given. The importance of evaluating the advantages and disadvantages of a transfusion *in each case* cannot be stressed enough. Furthermore, a careful assessment of the amount of blood needed for each situation is equally important. Every additional bottle transfused increases the possibility of harming the patient.

Ill effects may occur immediately as in the following example:

Mr. C was admitted to hospital with an embolus occluding the left brachial artery. He had a history of chronic rheumatic heart disease with mitral stenosis, and atrial fibrillation. After removal of the embolus he was given anticoagulant therapy, with dicoumarol. Ten days after operation he had a sudden severe gastrointestinal haemorrhage and became shocked (blood pressure = 80/40). His prothrombin time the day before was 53 seconds (normal = 12 sec.). During the next thirty hours the patient was given fourteen bottles of whole blood. His condition improved, blood pressure rose to 116/80, and all appeared to be well when he suddenly developed congestive heart failure with acute pulmonary oedema. Emergency measures to relieve cardiac embarrassment were taken (elevation of head, oxygen tent, tourniquets, etc.) and within a few hours he recovered from this crisis. There was no further bleeding and the patient was discharged after several weeks of convalescence.

This case, which could easily have been fatal, illustrates the danger of "overloading" the circulation, even when blood transfusion is clearly required to save life. Too much blood given too fast is very likely to cause acute pulmonary oedema especially in a patient whose heart is already weakened by disease. The example also illustrates the difficulty that may be encountered in finding a balance between too much transfusion and too little. In patients in shock, when blood must be given rapidly, the best guide to the amount to give is the venous pressure as indicated by inspection of the jugular veins.

The volume transfused may be decreased significantly by using packed cells rather than whole blood, when raising the haemoglobin is the effect desired.

Other harmful consequences of blood transfusion do not become apparent for some time:

Mr. B was admitted to hospital on October 5 with a urinary infection for which he was given antibiotics including Chloromycetin. His urinary condition improved, but twelve weeks later he was found to be severely anaemic. Bone marrow examination showed an aplastic anaemia which was believed to be drug-induced. He was transfused with sixteen bottles of blood during the following week and was later discharged having made a good recovery from the anaemia. In April, 155 days after transfusion he was readmitted because of rapidly deepening jaundice. It was concluded that the patient had transfusion hepatitis ("homologous serum jaundice"), which has an incubation period of 60–160 days. He died five weeks later.

The foregoing is an example of the circumstances in which a transfusion

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EDITOR'S NOTE: Mr. Spitzer was working at the Toronto General Hospital Blood Bank this summer. He had just completed his first medical year at the time of writing.

which is clearly indicated is nevertheless responsible for the death of the patient. In spite of the precautions taken by the blood donor service in questioning donors for a history of jaundice, the blood-transfusion resulted in fatal hepatitis.

Some ill effects of transfusion may go unnoticed for a long time, in some cases for many years:

Miss D, age 37, suffered from sickle cell anaemia. From age 16 she had required blood transfusions on several occasions, when her haemoglobin fell to low levels. The first transfusion had been uneventful but on two recent occasions she suffered severe transfusion reactions accompanied by long periods of anuria. Detailed investigation of her serum was made including the highly sensitive indirect Coombs test, and she was found to have a powerful irregular antibody (anti-Fy^a of the Duffy blood group system) with a titre of 1:1024. This antibody is capable of destroying transfused cells containing the corresponding antigen. The patient was Fy^a-negative. The antigen Fy^a is found in 65% of white Europeans.

This case illustrates the necessity for careful compatibility ("crossmatch") tests, employing sensitive methods. Some irregular antibodies can be detected only by the indirect Coombs test; with its use the previous transfusion reactions could have been avoided. This patient became sensitized in the course of the blood transfusion necessary for the treatment of her anaemia. The risk of sensitization increases in proportion to the amount of blood used, and this fact should be borne in mind when determining amounts of blood prescribed in treatment of disease.

In some circumstances there is not time to perform careful blood grouping and crossmatching, with all the checks and safeguards that provide maximum transfusion safety. Sometimes the critical condition of the patient demands that certain "short cuts" be taken for the sake of speed. Some tests must be curtailed and often omitted. Determining to what extent these measures are justified is a difficult problem that must usually be solved in a few minutes. The risks of transfusion discussed in this paper increase significantly when a crossmatch is not performed, and blood issued with only a brief emergency crossmatch is risky, though safer than uncrossmatched blood. Sometimes however it is certain that death will result almost immediately if blood is not given, and in such cases it is necessary to risk incompatibility or sensitization of the patient by giving uncrossmatched group O Rh negative ("Universal Donor") blood. However, when five or ten minutes are available, it is highly desirable to determine the blood group of the recipient, because, contrary to what is commonly believed, O Rh negative blood is not really "universal". The anti-A and anti-B substances present in group O blood agglutinate and may haemolyze the cells of group A, B, and AB recipients. When given in small amounts the harmful effects are usually avoided because of the dilution of these haemolysins from the donor in the recipient's circulation, but a fatal reaction may be caused.

In addition to the dangers mentioned, other hazards are involved in blood transfusion. Errors are possible in the many links of the chain of events that take place from the time the physician signs a requisition for blood to the time the patient is transfused:

On the day before her operation Mrs. E was told that a blood transfusion would be given in the operating theatre. When she remarked that no blood specimen for testing had been taken from her, the nurse in charge telephoned the Blood Bank and found that a specimen bearing Mrs. E's name had in fact been received there. This blood specimen had been found to be group A Rh negative and three bottles of the same group had been prepared for Mrs. E to be given the next morning. A blood sample was then taken from Mrs. E and was found to be group O Rh negative. In the subsequent investigation it was found that the first blood specimen had been taken not from Mrs. E but from an unconscious patient in the adjoining room because the requisition bore the wrong room number.

Had this group O patient received the group A blood under anaesthesia she would have surely suffered a fatal reaction. This example illustrates the great importance of careful identification of the patient from whom blood specimens are taken. Special precautions are indispensable when the person is unconscious.

Errors may also occur in the laboratory. Several emergency requests for blood may arrive in the Blood Bank in close succession when only one technician is on duty, and there may be repeated telephone calls from the wards concerned. It takes an intense effort of concentration to group and crossmatch blood for several people at the same time, and under the distracting circumstances described it is understandable that mistakes occur at times. The mistakes most likely to occur in the laboratory are clerical rather than technical. One would naturally be inclined to think that clerical errors can be attributed solely to carelessness. Yet, the volume of blood transfused in some hospitals is such that the demands of meticulous accuracy exceed human limitations.

Severe reactions have been known to occur using blood that has been mishandled in the wards by freezing or storing it improperly. Many hospitals have inadequate facilities for blood storage in the wards and operating rooms. Blood Bank refrigerators are maintained at temperatures from 3.5 C° to 4.5 C°. Blood should be always stored at a temperature within that range. Frequent removal of it from the refrigerator favours haemolysis and consequent reactions. Therefore, it is important when possible, not to order more blood than can be transfused without question. This prevents cancellations, re-crossmatching and unnecessary handling.

A leading Canadian blood group serologist, Dr. Bruce Chown of Winnipeg, writes some very interesting remarks that are appropriate as a conclusion to this paper:

"Why do you transfuse? Why *do* you? Why do *you*? What is the proof that more than a small fraction of the blood that is daily poured into patients in the operating room alters the prognosis for the better? Blood has always had a mystical quality; its use in the operating room is more often mystical than scientific. And for women! Most transfusions given to women under the age of 45 are given in relation to pregnancy—for the bleeding associated with an abortion, with a vaginal delivery, with Caesarean section, even, God save the meek, for simple anaemia. I would hazard the guess that not 5%, no, not 1% of transfusions so given have been life-saving. And I would hazard the guess too that at least as great a percentage has been death-dealing." (C.M.A.J., 77, 1037, 1957.)

TAKING THE PLUNGE: REFLECTIONS UPON THE WEBSTER PRIZE ENTRIES

T. P. MORLEY, F.R.C.S.

NOW that my three years as adjudicating member of the Webster Scholarship panel is over I feel at liberty to make a few random and strictly personal observations. As I read the articles in this journal I was reminded of much that I had forgotten and introduced to more that I had never known, and it was clear to me that the inspiration behind

EDITOR'S NOTE: The Webster Prize ($50.00) is awarded annually by the Academy of Medicine for the best article published in this Journal written by an undergraduate.

the Webster bequest, the editorial policy of the Journal and the enthusiasm of the contributors were all working with obvious success towards the common goal of undergraduate authorship.

During these years the standard of writing has risen while the level of knowledge, always high, has remained about the same. Factual errors have occurred from time to time and there have been serious omissions, but in the great majority of cases the authors' knowledge of their subjects has been clearly apparent. All the authors will agree that ignorance was never the stumbling block —recourse to a library or teacher smoothed the path of knowledge; the halting phrase, the fumbling pen, the elusive word, these were the exasperations that allowed no peace of mind. It is concerning this aspect of authorship that these few remarks are made.

Writing is one of the oldest forms of self-expression (drawing and music-making are older) and there is no shortage of advice on how it should be done. But just as no one learns to swim without taking the plunge, so no author becomes a writer without first submitting his immature scribblings to the soured scrutiny of an editor and, if he is fortunate, to the casual glance of an uninterested public. Without determination the tyro is soon discouraged. What seems so effortless for others turns out to be easy only in his dreams. The more he studies his chosen art the greater his disillusion and his first article which was to have been a mature and, in places, brilliant treatise shrinks to a clumsy composition whose only message seems to be that the man who wrote it should not advertise his incompetence. But his vision was conception, his humiliation labour; without these life could not begin.

Those who have crossed the threshold will acknowledge the general truth of what I have said and these sentences will be of passing interest only. To the others I need only state two rules: 1. Have something to say. 2. Say what you mean. Keep to these and all else follows. It is on Rule 2 that so much has been written. Famous commentaries include Fowler's "Modern English Usage" and "The King's English", Partridge's "The Concise Usage and Abusage" and Gowers's "Plain Words". (The last has the merit of being very cheap. It is published by Her Majesty's Stationery Office.) Dictionaries are indispensable but it will be remembered that American and British English meaning and usage are sometimes quite different; just how different they may be is shown in a little dictionary called "American into English" by Carey. A guide book may make good reading if it is well written but it is studied to greatest advantage in conjunction with a visit to the country which it describes. So it is with authors' vade-mecums and compendia; they take their proper place in the presence of great literature. A third basic rule might be added: To have read and admired the works of the immortals. The appreciation of literature is largely an emotional experience and its impact on us is slight unless we have been lost in admiration at the beauty of the works we have read. Good writing comes from a constantly critical attitude towards everything we read, but the critical faculty withers if it is nourished exclusively on a deficient diet. There must also be a determination always to write well. The language of techniques, trades and professions is none the less elegant for being terse and apposite, and it is certainly more effective. Unnecessary jargon (technical jargon is necessary up to a point), confusion of thought and expression, bad grammar and syntax, the striking of poses, all alienate the author from his readers.

Our best endeavours should not be reserved for prize essays and examinations. Most people who write badly never try to write well. In the busy life of the

medical student lecture notes form one of the mainstays of his instruction, but they are only notes and if they become more elaborate they have ceased to serve their purpose. Unfortunately, for years on end these notes comprise the only writing exercise that the student enjoys. No wonder he may become inarticulate. The clinical student, however, has in his case histories a splendid opportunity to exploit his latent literary talents and to impose literary self-discipline. Here, without judgement by examination hanging over him, he can practise the art of composition which as an educated man it is his duty to develop and improve. He can work to his own standards and towards his own ideals rather than to what he hopes is someone else's. Observation, sympathy, human experience, clinical acumen, scientific knowledge, logic and judgement are all required in the assessment of a patient and will take their place in the final written record.

However wretched his literary sallies may appear it is the conviction that lucid self-expression is important to him that will keep the student's determination alive in the face of disappointment. He cannot write well in public if he fails to do so in private—and for most of us nine-tenths of what we write is for our own eyes. The compilation of case histories will therefore be his chief literary discipline and the pursuit of self-discipline is one of the major preoccupations of a university. What, therefore, could be more appropriate to foster this aspect of undergraduate training than the creation of the Webster Prize? The challenge has been eagerly taken up and the perennially unsuccessful struggle for the prize itself by the whole field but one is not in vain.

A few points that the essays brought to mind may be mentioned concerning the technique of writing. 1. *Style.* A conscious attempt to develop a style is apt to become self-conscious. Style is an unconscious sequel to good, plain writing; and in case the critic does not already know it, the easier a passage is to read the harder it has been to compose. Follow Rule 2 and say what you mean. 2. *Abbreviations.* "At 5.45 the O.R. was phoned . . ." "O.2 Gm. t.i.d.p.o." In some centres O.R. refers to the Obstetrical Resident, not the Operating Room. T.i.d.p.o. is acceptable when it is part of a formally written prescription but not when it appears in a line of text; it is reminiscent of lecture notes. 3. *Proof reading.* Editors are better proof readers than authors, but the author cannot relinquish this function. Many slips corrected by the editor would be missed by the author but the editor is in no position to correct errors of fact. Nor is it the editor's function to ensure that references are correct. There is no excuse for misspelling the name of an authority listed in the references; it is tactless to do so when he is one of your senior teachers and future examiners. 4. *Slang; colloquialisms.* Slang creeps in easily and may be difficult to keep out. For example, "the findings of X and Y *would* seem to support this view." Of all the colloquialisms "of course" is the hardest worked. 5. *Unintentional and double meaning; obscurity.* The description of Mrs. A. B. as "a 40 year old . . . separated waitress" leaves the reader uncertain what she had been separated from. Again, "any swelling of the body of the testis should be held suspect" may convey a meaning that the author did not intend.

John Dixon Webster made his bequest to the Academy of Medicine of Toronto. The Council of the Academy decided to devote the annual interest from the capital sum to the granting of what is now known as the Webster Prize. The eagerness of the competitors and the improved standard of writing that they have achieved are sufficient recognition of Dr. Webster's munificence and the Academy's wisdom.

THE PLACENTA REVIEWED

J. H. WAIT, 6T0

Definition

The placenta is defined by Mossman as "any intimate apposition or fusion of the foetal membranes to the maternal tissues for physiological exchange". In man it is classified as a deciduous discoidal placenta of the haemochorial type.

Anatomy

(i) gross

About the seventh day after fertilization the ovum undergoes interstitial implantation into the richly vascularized receptive endometrium. The trophoblast, as the first embryonic membrane, covers the entire surface of the ovum. It secretes cytolytic enzymes to become invasive, with that portion over the embryonic cell mass being most active. The ectodermal trophoblast becomes fused with the mesodermal allantois to form the chorion. As the maternal venules, capillaries and arterioles are progressively invaded by the eroding trophoblast, intercommunicating intra- and inter-cellular vacuoles called lacunae, in which maternal blood sluggishly circulates, are developed. This labyrinth of lacunae lined by trophoblast forms the intervillous spaces. Initial nourishment results from absorption, by the syncytial layer of the trophoblast, of the local breakdown products of the endometrium. This is histotrophic metabolism and is very brief in duration compared with haemotrophic metabolism and direct nourishment from the placental circulating maternal blood.

By the fourteenth day the trophoblast is composed of two layers, an inner cytotrophoblast and an outer syncytiotrophoblast. Initially the latter undergoes the more active growth, forming trabeculae which may be termed primitive syncytial villi. By the eleventh day, the cytotrophoblast grows into these syncytial projections forming primary chorionic villi. In the third week mesoderm invades these epithelial cellular buds forming secondary chorionic villi. Finally an arterio-capillary-venous system develops in the mesenchymal core of each villus and becomes functionally connected with the embryonic heart to form tertiary or definitive functioning villi. Some villi become connected to the basal plate by means of proliferating solid cores of cytotrophoblast and are therefore called anchoring villi. Others hang freely in the intervillous space. The villi are marked off by placental septa into lobules known as cotyledons. These septa penetrate about two thirds of the placenta from the basal plate and never reach the chorionic plate. They are not presently considered as fluid-tight partitions and are richly perforated. They develop from foetal trophoblastic tissue and do not contain vessels.

The chorion is divided into two parts, the chorion laeve and the chorion frondosum. The villi related to the chorion laeve are apposed to the decidua capsularis, that portion of the endometrium which overlies the ovum and separates it from the rest of the uterine cavity, and these villi become compressed and degenerate. The chorion frondosum is composed of highly vascularized, multibranched villi and is apposed to the decidua basalis. The functional placenta is thus composed of the chorion frondosum and the decidua basalis.

(ii) microscopic

The syncytiotrophoblast is composed of cells with brush borders and nuclei with no separating membrane. The cytotrophoblast or Langhan's layer is composed of discrete cuboidal cells of clear cytoplasm and is regarded as the germinal zone of the outer syncytial layer as well as the mesoderm of the chorionic

villi. The Langhan's cells are characterized further by an interstitial matrix which surrounds and separates these cells from one another. This intervillous matrix is classically referred to as Fibrinoid Material, a mixture of blood fibrin, tissue fibres and stroma cells. After the third month of pregnancy the Langhan's cells disappear and can only be detected by the electron microscope. Also as gestation progresses the syncytial layer forms an attenuated membrane over the villi, the villi become more numerous and the foetal capillaries within the tertiary villi increase in number. Therefore an increased filtering surface composed only of a separating membrane of foetal capillary endothelium, a delicate network of argyrophilic reticular fibres and the syncytium results.

Consider now the endometrium. There are several characteristic cells of pregnancy. One is the Hofbauer cell found predominantly in the early stages and considered to be phagocytic. The other is the decidual cell, an endometrial perivascular connective tissue cell which enlarges in the presence of a functioning corpus luteum to become rounded or polyhedral. These cells function as localized areas of specific chemical transformation and accumulate glycogen, lipoids and pigments within their cytoplasm. The decidual cells undergo hyaline degeneration with the advance of pregnancy as part of the decidual or stromal reaction. At parturition the decidual tissue forms a cleavage zone with the shedding of the endometrial material. This may be important in preventing excessive haemorrhage.

Placental Circulation

Essentially, vascularization of the human placenta represents a haemochorial condition characterized by immediate contact between the circulating maternal blood and the epithelium of the chorion.

(i) maternal circulation

Bumm believed that the tortuous maternal arteries enter the placental septa and open out into the intervillous space where the maternal blood is thus washed around the floating villi in direct contact with the chorionic epithelium. After the blood has flowed through the intervillous space, the venous outflow takes place through the basal plate in the same cotyledon thus forming a maternal circulatory unit.

Spanner using corrosive specimens envisages overflow filling of the placenta with arterial blood which is introduced into the intervillous space by the spiral arterioles and rises between the septal walls in the placental labyrinth to the subchorial lake, before spreading laterally to the marginal sinus which surrounds the entire free edge of the placenta and through which all venous drainage of the placenta takes place. The central lobules have no venous connections.

Through the intensive scientific work of Ramsey the maternal circulation has been shown to combine features of Bumm's and Spanner's theories. To show how the endometrial vessels adapt themselves to the conditions of pregnancy, she uses Rhesus monkeys palpated for ovulation and bred at specific dates. On the desired day of pregnancy colloidal mercuric sulphide is injected into the intact unanaesthetized animal via the femoral vein and the uterus and adnexa are then fixed in situ. Large blocks are cut from representative portions of the uterus embracing the full thickness of the placenta. She describes the main uterine arteries as passing to the mid-myometrium where they break up to form a circumferential wreath of arcuate arteries. Radial arteries coming off the arcuates branch into two types of endometrial vessels, the basals which are insensitive to hormonal changes, and the spiral arterioles which are sensitive to ovarian hormones and which coil upward toward the endometrial surface, entering the intervillous space through a central outlet in each cotyledon. As the cycle progresses, the spiral arterioles increase in length and

become increasingly coiled. If pregnancy intervenes and, concomitant with trophoblastic invasion, hormonal support is not lost the spiral arterioles do not go into spasm and no menstrual slough is formed. With the opening up of more spiral arterioles and the decrease in endometrial thickness from pressure and encroachment of the overlying conceptus, these vessels undergo more coiling and lateral looping. About the twentieth week accommodation occurs when the uterus stops growing and starts stretching to make room for the developing foetus. The coils of the spiral arterioles become "paid out like coils of rope on the deck of a boat". There are also changes in the walls of these arterioles. With the beginning of erosion they reveal an endothelial proliferation and resulting decrease in the calibre of the lumen. There is also gradual replacement of the muscle cells in the media and adventitia by epithelioid cells. The final change is intimal fibrosis beginning by the eighth week and thereby decreasing the number of arteries communicating with the intervillous space.

The venous system adapts to both the growth and stretching phases of uterine enlargement chiefly by passive changes in calibre. The number of venous exits from the intervillous space also decreases as pregnancy advances.

Ramsey does not deny the existence of a marginal sinus, but suggests it is not the only venous exit. It is the marginal portion of the intervillous space bounded laterally by the chorionic membrane, below by the trophoblastic plate and above gradually merging with the subchorial lake. This structure is maternal in origin. Ramsey visualizes central basal drainage channels for each cotyledon, often lying fairly close to the arterial entries.

On physiological consideration of maternal placental circulation Ramsey sees the impetus for the rise of afferent blood toward the subchorial lake caused by the haemodynamic force of the high maternal blood pressure augmented by the intermittent constriction of the spiral arterioles and myometrial contractions, sometimes referred to as Braxton-Hicks contractions. The convergence of efferent streams upon venous exits results from the higher pressure within the intervillous space compared with venous pelvic pressure.

(ii) FOETAL CIRCULATION

Bumm describes the villus as an inverted "deliquescent tree" with its roots in the chorion and many twigs at its summit fused with the decidua as anchoring villi. Spanner sees the villus as a "weeping willow" with branches curving back after anchoring in the decidua carrying long straight venules toward the chorion.

Foetal placental circulation has been extensively studied by Boe using tissue visualized under stereoscopic microscopy in order to follow the course of the finer vessels. The vessel-carrying organs are the foetal stems of chorionic tissue with the truncus chorii forming the base of the chorionic tree in each cotyledon. The quantity of villi increases as the size of the stem decreases, and therefore most villi are at the peripheral areas of the tree.

Beginning with the umbilical cord there are two arteries with solid muscular coats lying superficial to the single vein. The vessels follow the characteristic spiral of the cord. On reaching the chorionic plate the arteries divide into major intercommunicating branches which run radially but never within a common sheath. Having completed their separate courses in the chorionic plate the artery and vein meet again and run parallel in a common sheath. Terminal division of the stem vessels results in a single artery, capillary and vein for each villus, forming a circulatory unit. The arteries run long distances superficially in the stems before curving away to enter the terminal villus. Veins do not run retrograde courses but take the shortest route to the collecting vessels.

The vascular pattern consists of branches of stem vessels, the paravascular capillary network (PVCN) and the capillary network of the terminal chorionic villi. The capillary network comprises a reticulum formed by supply and outlet capillaries and sinusoidal expansions with cross-anastomoses. It alone functions for metabolic exchange. The paravascular capillary network is composed of an elongated network of vessels of capillary size preceding the functional capillary network and acting as an arteriovenous communication. It acts as a buffer system preventing overloading of the villous circulation. The major chorionic structures and terminal villi receive a separate artery plus supply vessels from the PVCN and have a separate vein.

Physiologically the increase in diameter of the umbilical arteries as they enter the chorionic plate, the tendency of foetal arteries to pre-divide inside the stems and terminal branches, the characteristic difference in this pattern of the arteries and veins, and the make-up of the PVCN serve to reduce the rate of blood flow but not to lower the pressure. The pressure remains high until the level of the PVCN. Because of a sphincter at the start of the ductus venosus the pressure is also high in the umbilical vein, about 30–40 mm. Hg. Therefore the placental capillary vessels are under high pressure, greater than in the intervillous space.

The Placenta as an Organ of Transfer

Essentially the placenta transfers carbon dioxide and water from the foetus to the mother, and oxygen and nutritives from the mother to the foetus. Originally this process was considered one of physical diffusion through a semi-permeable membrane. However, today the tissue barrier is not considered inert but metabolically active as judged by its rate of utilization of oxygen which is equivalent to that of the kidney and also by its enzymatic contents. There are several other factors involved in placental permeability. The intimacy of the contact of the two bloodstreams allows a more rapid rate of transference of substances like the sodium ion. Secondly, as pregnancy advances there is an increased surface area for maternal blood, a thinning of the villous coat and decreased cellularity of the capillary walls to accommodate the necessity of the placenta supplying an increasing mass of foetal tissue.

Oxygen and carbon dioxide are exchanged through a differential tension mechanism. Large molecules such as proteins, polysaccharides, fats and nucleic acids are synthesized *de novo* within the foetus from smaller molecules, amino acids, monosaccharides, glycerol, which are transferred from maternal blood by an active energy-consuming process. Water soluble vitamins are transferred more readily than fat soluble vitamins. Metabolites such as urea, uric acid and lactic acid also pass readily, as do narcotics, barbiturates and general anaesthetic agents. Some plasma proteins such as the gamma globulins are transferred in whole and are responsible for the dangers of Rh isoimmunization. However Brambell has recently proven in rabbits that immune globulins may also cross the foetal membranes into the amniotic fluid, and thence to the foetus via the respiratory or gastro-intestinal epithelium. The concentration of amino acids, calcium, phosphates, most vitamins, especially ascorbic acid, and many other substances is higher in foetal than in maternal blood. The advantage to the foetus to have these nutrients for growth present in high concentrations is obvious.

Hormonal Functions of the Placenta

This is a subject which is being intensively studied presently.

(i) chorionic gonadotrophin hormone (CGH)

CGH is produced by the cytotrophoblastic cells. It is a glyco-protein of molecular weight 60,000. Its curve of excretion and blood levels follows the rise and decline of the Langhan's cells. This

hormone first makes its appearance about the fourth week, reaches a peak by the ninth week, falls gradually to low levels by the thirteenth week where it remains until parturition. Its function is to maintain the corpus luteum in the production of oestrogen and progesterone, which keep the endometrium suitable for nidation, until the placenta is ready to assume their secretion. CGH forms the basis of the bio-assay tests for pregnancy such as the Aschheim-Zondek and Friedman.

(ii) PROGESTERONE AND OESTROGENS

Progesterone is assumed to be produced by the syncytiotrophoblast. The evidence for the production of progesterone by the placenta lies in the experimental removal of the ovaries in the latter part of gestation without terminating the pregnancy.

Oestrogens are found in the human placenta in high concentrations and extracts of the placenta cause oestrogenic responses when injected into immature mice. In the monkey the removal of the ovaries as well as the foetus was ineffective in altering the excretion rate of urinary oestrogens but expulsion of the placenta caused a drop to non-pregnant levels. After the first two months of pregnancy the curve of excretion of both oestrogen and progesterone rises progressively but falls precipitously at parturition.

(iii) OTHERS

The placenta is also said to produce adrenocorticotrophin-like hormones, androgens and relaxin. It is no longer considered to produce aldosterone and corticosteroids (compounds E and F). The increased levels of these hormones result from an increased binding power of the serum proteins and a decreased degradation rate by the liver.

The present thought is that the placenta does not have the many endocrine functions originally attributed to it.

SUMMARY

The author has presented the placenta's anatomy, circulation and hormonal function with reference to past concepts and present research.

ACKNOWLEDGEMENTS

The author would like to extend his sincere thanks to the understanding and encouragement received from Dr. Wm. Paul of the Toronto Western Hospital and Dr. Elizabeth Ramsey of the Carnegie Institution, Baltimore.

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SUMMER INTERNSHIP IN A SMALL COMMUNITY

D. F. BUTT, 6T0

MANY jobs in a number of hospitals, large and small, are available to medical students who have completed their third medical year. A large percentage of students avail themselves of such an opportunity and usually find the experience invaluable since at this relatively early stage in his medical career, the young "doctor" is able to carry out many of the procedures used in routine medical practice. Some students choose the larger specialized hospitals such as

psychiatric hospitals, however for the person who wishes to obtain experience in a general practice of medicine, the smaller country hospital perhaps has more to offer. It is this smaller unit, away from the ready availability of the skills of a more highly trained team, about which this article is concerned.

In the year 1901, Dr. H. C. Wrinch, from Toronto Medical School, made his way up the swift Skeena River in Northern B.C. to serve the native Indians at Hazelton. To-day a fifty-eight bed hospital stands in his memory, staffed by two doctors and ten nurses, whose services are available to the three thousand population. Three quarters of these people are natives. The staffs' salaries are paid by the United Church of Canada, although to as great an extent as possible the hospital is self-supporting; of course the Indian Health Services, and the B.C. Health Insurance Service help the economic situation. Through the aid of various auxiliaries and other organizations many of the necessities such as a microscope are supplied.

Wrinch Memorial Hospital is nestled in a valley near the junction of the Skeena and Bulkley Rivers, surrounded by snow-capped mountains. In spite of the northern altitude, the summers are similar to those in Ontario, except that there is a notable absence of the oppressive humidity found here. Although the temperature occasionally climbs to 95° or 100° Fahrenheit, few complaints are heard about the heat.

The hospital is a three story edifice housing the usual necessities essential to good quality health services. X-ray equipment, E.C.G., an anaesthetic machine, and a modern laboratory are regularly used, in contradistinction to the popular misconception that a "Mission Hospital" is a thatched roof hut with a single ward full of malaria patients, and staffed by a few under-fed nurses and a doctor.

The operating room and emergency were in use much of the time during the summer. On the ground floor of the hospital are situated two well-equipped doctor's offices, in use each afternoon from two o'clock until anywhere from four-thirty to seven or eight at night. At the time of writing, an addition is being planned for new doctor's offices, reception, admitting and emergency.

Wherever there are people there are "interesting patients". One need not spend his life in a large teaching center to see and treat patients with unusual conditions, although naturally there is a greater aggregation of unusual diseases found in the larger hospitals. Hazelton, and surrounding area was not lacking in interesting cases in Medical, Paediatric, Surgical, Obstetrical and Gynaecological services.

One could well call this valley the "fertile belt" and not be far wrong when referring to obstetrics. There were approximately twenty-five deliveries during the summer, including a Caesarean section on a young woman with placenta praevia and twins. Many of the grand multiparas with twelve children at home, push their infants out so quickly that the doctor has to muster all his athletic ability to arrive at the bedside in time, and often the race is lost by the physician. However forceps do have to be used occasionally.

It is in paediatrics where one does not see many of the conditions discussed so enthusiastically at Sick Children's Hospital. Perhaps seventy per cent of the patients in the paediatric ward had diagnoses of "upper respiratory infection" and "otitis media"; others included "P.U.O.", "Enteritis" and "T.B.", etc.

Surgery was confined to relatively simple procedures, and performed by the staff of the hospital. Tonsillectomies, multiple teeth extractions, wound repairs, hernia repairs, Caesarean sections, appendectomies, and other abdominal emergencies were carried out, but patients requiring more extensive operative techniques were flown to Vancouver.

Medicine was also varied, but less

dramatic. Several myocardial infarctions were treated, chest conditions, especially pneumonia, bronchiectasis, T.B., and asthma were fairly common. Probably the most common condition among the native adults was rheumatoid arthritis. Students can learn a great deal by caring for these people. Other conditions included thrombocytopenic purpura, tuberculous pericarditis, Guillain-Barré Syndrome, carotid artery thrombosis, etc.

The duties of the student are not clearly defined. However, due to the departure of one of the three physicians at the first of the summer, many opportunities arose which initiated one into the practice of medicine. Morning activities consisted of rounds, surgery, and time devoted to one's own patients in hospital, depending upon the day of the week; afternoons were generally reserved for out patients. During the afternoon between ten and thirty patients would be seen by the doctor on duty and the student. One afternoon per week a clinic would be held at one of the native villages up to forty miles away, and to this the student would go regularly. One aspect of training acquired that is not likely to be derived from the city hospitals was the fine art of pulling teeth. The dentition of the native inhabitants is generally poor, and adequate opportunity is afforded for tooth extraction. Of course the student has excellent chances to perform many of the physician's functions, but he is under supervision of a staff doctor. In this way he is able to learn a great deal of the practical aspects of every day medical practice.

Although considerable time is devoted to hospital work, including some nights on call, there is much in the way of inexpensive extra-curricular activities available. For those who enjoy hunting, fishing, swimming, golfing, mountain climbing, hiking, camping, photography, or just plain visiting, an area such as Northern B.C. has a great deal to offer. The pace of living is considerably slower, and one finds the usual pressures of city life are lacking. This being a Church-supported organization, some time is devoted to Church work but the student is not expected to participate in "evangelizing"—just to live by the ethics of his chosen profession, which in most cases are indistinguishable from those of the Church.

Thus, for a medical student, desirous of discovering the nature of a practice in a small community with the conveniences of a hospital, a junior internship following third medical year is invaluable. Such an internship has more to offer than merely indicating to a person whether he will be suited to this type of practice; it is a discovery of a way of life, a philosophy of the practice of medicine. We in the city have been encumbered so by books and clinics, and in spite of the efforts of our teachers, we often have slipped into the habit of regarding a disease as all important, tending to neglect the patient as a person. In a small area, the technicalities of medicine are in their proper perspective—taken for granted that they have been mastered. The kind of person the Doctor is, governs the degree of his success.

ABSTRACTS

EVALUATION OF RADIOACTIVE IODINE (I^{131}) AS A TREATMENT FOR HYPERTHYROIDISM. Carl E. Cassidy and E. B. Astwood. The New England Journal of Medicine. 2, 261, July 9, 1959.

Radioactive iodine, although an effective form of treatment for hyperthyroidism has the disadvantage that response of patients to a selected dose varies widely. As yet no method has been devised to select a dose that would be uniformly satisfactory. A quantity that may restore normal thyroid function in one patient may prove entirely ineffective in another, and a similar dose may even induce lasting myxoedema in a seemingly comparable case. This study was made in a search for factors or influences that might lead to a better understanding of individual variability.

Two hundred patients (age 21–78 years) with hyperthyroidism were observed from one to seven years after treatment with radioactive iodine. Sixty-five per cent responded to one dose, and 89 per cent were cured after two treatments; 84 patients had no previous treatment, 86 had recurrent hyperthyroidism after medical and surgical treatment, and 30 had been treated with antithyroid drugs elsewhere. The initial dose was calculated by the formula:

Dose in microcuries $=$ 10,000 $\times$ physical half life $\times$ 100 $\times$ weight of thyroid $\div$ 160 $\times$ effective half life $\times$ 24 hour uptake (per cent)

Severe cases received antithyroid drugs following radioactive iodine.

RESULTS: Normal thyroid function returned in 85.5 per cent of patients and permanent myxoedema developed in the remaining 14.5 per cent. Temporary myxoedema appeared from 3–8 months after treatment in 7.5 per cent of patients. Neither radiation thyroiditis nor an acute exacerbation of hyperthyroidism after the therapeutic dose was seen during this study. None of the 200 patients exhibited a recurrence.

Although most dosages of radioactive iodine were calculated by the above formula results were no better than those obtained by one or other arbitrary methods of dosage selection. Although generally larger goitres required larger doses, in some cases little relation between thyroid size and required dosage was seen. The nodularity or diffuseness of the goitre made no difference in the result.

Adjuvant therapy with antithyroid drugs did not decrease the effectiveness of the isotope in the sense that the need for future treatment was increased but there were fewer resultant cases of myxoedema when antithyroid drugs were also used.

No support was found for the clinical impression that hyperthyroidism in males is more resistant to treatment.

It is the opinion of the authors that radioactive iodine therapy is superior to surgical treatment in that although it shares the hazard of myxoedema there is no mortality, no vocal cord paralyses, no tetany, no scarring of skin, and a negligible chance for recurrence. Currently there is much concern regarding the hazards of radiation, and authoritative statements cannot be made on this subject. It can be said however, that in this series, no cases of leukemia have been observed and no thyroid alterations that could be construed as neoplastic have arisen.

E.J.H.

NEWS AND NOTES

Professor W. R. Winterton, F.R.C.S. has come to the University of Toronto as an exchange Professor in Obstetrics and Gynaecology, from the Middlesex Medical School. He will be here for the month of October.

Sir Eric Riches, a distinguished surgeon from the Middlesex Hospital Medical School will also visit the University of Toronto Medical School in October.

The Dean of Medicine, Dr. J. A. MacFarlane, and Dr. W. B. Spaulding of the Department of Medicine attended the Second World Conference on Medical Education in Chicago, in early September.

Dr. and Mrs. J. A. MacFarlane invited the members of the Medical Society and the executive of the Physical and Occupational Therapy Association to supper at their farm, St. Fillans, near Terra Cotta, on Saturday, October 3.

Professor J. H. Kellgren, F.R.C.P., the Director of the Rheumatic Research Centre of Manchester University, visited the University of Toronto in October. He lectured at Sunnybrook Hospital and also the Toronto General Hospital. He delivered the 1959 annual Lecture in Rheumatic Diseases on Friday, October 16 in the Toronto General Hospital. This Lecture is sponsored by the Canadian Arthritis and Rheumatism Society. His topic was the "Differential Diagnosis of Polyarthritis".

Professor George L. Montgomery, Professor of Pathology from the University of Edinburgh lectured on "Chronic Thyroiditis" in the Banting Institute on October 2, 1959.

Many members of the Faculty were able to attend the Joint Convention of the Canadian Medical Association and the British Association in Edinburgh, Scotland, this past summer. The program was presented half by Canadians and half by the British. Many of our faculty took part in the various symposia and panel discussions.

"McGill cuts their medical course by one year starting this fall," said Dr. Lloyd Stevenson, Dean of the Faculty of Medicine at McGill. He said that the reduction from eight years to seven years of undergraduate and graduate study will not mean a relaxation of standards. At the University of Toronto Medical School the majority of students get their degrees in six years. Students entering the first medical year from other degree courses have spent an extra year or two obtaining their degree, but must still complete four medical years. In the Province of Ontario there is one more year of High School than there is in the Province of Quebec.

Dr. R. F. Farquharson, head of the Department of Medicine, visited Australia this summer. He visited all the medical schools, and hospitals in major cities where there were no medical schools. He conducted clinics, made rounds and lectured. In Sydney, Dr. Farquharson gave the Lambie-Dew Oration to a senior group of medical students. This oration is presented on an annual basis. He returned via Bangkok, and Cairo, New Delhi, Rome and London. The entire trip covered 28,000 miles.

On Wednesday, October 13, the first annual C.A.M.S.I. Lecture on Medical Education was given by Dr. J. H. Hamilton. Dr. Hamilton spoke at Falconer Hall.

The opening meeting of the Osler Society was on October 20. The guest speaker was Dr. Wm. Blatz, who spoke at Phi Chi Fraternity, 171 St. George St.

R.M.G.

ADDRESSES OF GRADUATING CLASS IN MEDICINE—JUNE, 1959

Allen, M.S., Toronto General Hospital, Toronto.
Anelevitz, I. C., New Mount Sinai Hospital, Toronto.
Armstrong, R. F., Toronto Western Hospital, Toronto.
Atkinson, Miss J. M., Toronto East General Hospital, Toronto.
Baines, A. D., Toronto Western Hospital, Toronto.
Bateman, C. R., Toronto Western Hospital, Toronto.
Becker, A. J., Toronto General Hospital, Toronto.
Bell, J. F., Wayne County General Hospital, Eloise, Mich.
Beranbaum, E. R., New Mount Sinai Hospital, Toronto.
Birkett, C. W., Toronto Western Hospital, Toronto.
Brown, G. M., St. Michael's Hospital, Toronto.
Burger, J. S., Toronto East General Hospital, Toronto.
Burgess, W. J., Ottawa Civic Hospital, Ottawa.
Butt, W. P., Toronto East General Hospital, Toronto.
Carlisle, R. V., St. Joseph's Hospital, Flint 2, Michigan.
Cecutti, A. G., St. Michael's Hospital, Toronto.
Chambers, H. R., Toronto East General Hospital, Toronto.
Chisholm, L. D. J., Toronto General Hospital, Toronto.
Cochen, A. R., Toronto General Hospital, Toronto.
Cohen, M., King's County Hospital, Brooklyn, N.Y.
Cohen, W. R., Cedars of Lebanon Hospital, Los Angeles, Cal.
Creighton, R. E. W., Toronto East General Hospital, Toronto.
Crotin, A. M., King's County Hospital, Brooklyn, N.Y.
Curry, R. H., Toronto General Hospital, Toronto.
Curtis, D. D., Toronto East General Hospital, Toronto.
Danis, J. J., St. Michael's Hospital, Toronto.
Davidson, H. A., Hamilton General Hospital, Hamilton, Ont.
Dennis, M., Harrisburg Hospital, Harrisburg, Penna.
Dickson, D. N., Grace Hospital, Detroit, Michigan.
Edelist, G. J., New Mount Sinai Hospital, Toronto.
Edmeads, J. G., Toronto General Hospital, Toronto.
Evans, J. C., Toronto Western Hospital, Toronto.
Ezra, P. S., Michael Reese Hospital, Chicago, Illinois.
Faught, K. A., Toronto East General Hospital, Toronto.
Finn, W. P. St. Michael's Hospital, Toronto.
Gold, G., New Mount Sinai Hospital, Toronto.
Gonsalves, C. G., Toronto General Hospital, Toronto.
Grader, J., New Mount Sinai Hospital, Toronto.
Grant, R. J., Toronto Western Hospital, Toronto.
Greenhow, P., Toledo Hospital, Toledo, Ohio.
Groh, Miss R. A., Huntington Memorial Hospital, Pasadena, Calif.
Grose, P. S., St. Joseph's Hospital, Toronto.
Grosfield, I. N., King's County Hospital, Brooklyn, N.Y.
Guest, R. G., Toronto East General Hospital, Toronto.
Haberman, H. F., Toronto General Hospital, Toronto.
Haldenby, D. A., Toronto Western Hospital, Toronto.
Hall, H. J. E., Toronton Western Hospital, Toronto.
Hall, W. C., Vancouver General Hospital, Vancouver.
Hallett, R. E., Tampa General Hospital, Tampa 6, Florida.
Harris, J. E., Toronto General Hospital, Toronto.
Heide, A. R., Fresno County General Hospital, Fresno, Calif.
Hiscox, P. E. A., Toronto Western Hospital, Toronto.
Hoffman, J., Toronto General Hospital, Toronto.
Hohenlohe, V., Hamilton General Hospital, Hamilton, Ont.
Holtzman, J. H., St. Michael's Hospital, Toronto.
Hooey, Miss M. A., Toronto Western Hospital, Toronto.
Hull, R. F., Mount Carmel Mercy Hospital, Detroit, Mich.
James, F. G., Toronto East General Hospital, Toronto.
James, H. P., St. Michael's Hospital, Toronto.
Kaczanowski, Miss M. B., St. Michael's Hospital, Toronto.

Kalinovski, R., Toronto East General Hospital, Toronto.
Kalkman, J. W., Toronto Western Hospital, Toronto.
Kelly, N. H., St. Joseph's Hospital, Toronto.
Keltz, I., New Mount Sinai Hospital, Toronto.
Kerbel, G. A., Toronto Western Hospital, Toronto.
Kerbel, N. J., New Mount Sinai Hospital, Toronto.
Kloster, R., Aust Agder Sentral Sykelmo, Arendal, Norway.
Knowlton, R. J., St. Michael's Hospital, Toronto.
Kosoy, M. H., University Hospital (Maryland), Baltimore, Md.
Kravitz, H., Cedars of Lebanon Hospital, Los Angeles, Calif.
Lansky, G. S., Toronto General Hospital, Toronto.
Larner, A. E., McLaren General Hospital, Flint, Michigan.
Lee, S. B., Toronto General Hospital, Toronto.
Levin, R. C., New Mount Sinai Hospital, Toronto.
Little, A. H., Toronto General Hospital, Toronto.
Little, B. J., Toronto General Hospital, Toronto.
Livermore, Miss M. L., St. Michael's Hospital, Toronto.
Loach, L. F. W., Toronto General Hospital, Toronto.
McAdam, W. M., Toronto East General Hospital, Toronto.
Macdonald, D. J., Toronto Western Hospital, Toronto.
McIntyre, W. C., University of Alberta Hospitals, Edmonton.
McNeill, O. R., St. Michael's Hospital, Toronto.
Maloney, J. D., Madison General Hospital, Madison, Wisconsin.
Margulies, A. I., New Mount Sinai Hospital, Toronto.
Milligan, J. E., Toronto General Hospital, Toronto.
Mitchell, D. P., Toronto General Hospital, Toronto.
Moldofsky, H., Toronto General Hospital, Toronto.
Moore, P. C. F., Hamilton General Hospital, Hamilton, Ont.
Morin, J. D., St. Michael's Hospital, Toronto.
Moscarello, Mrs. R., St. Michael's Hospital, Toronto.
Murdoch, D. A., St. Michael's Hospital, Toronto.
Neiman, S. L., New Mount Sinai Hospital, Toronto.
Newton, H., Toronto General Hospital, Toronto.
Nolan, P. A. T., St. Michael's Hospital, Toronto.
Paul, D. J., St. Michael's Hospital, Toronto.
Peacock, J. J. M., St. Michael's Hospital, Toronto.
Perkin, G. W., Toronto Western Hospital, Toronto.
Pierce, Miss G. B., Santa Barbara Cottage Hospital, Santa Barbara, California.
Porter, M. J., University of Alberta Hospitals, Edmonton.
Prince, W. R., Toronto Western Hospital, Toronto.
Procter, W. C., Hamilton General Hospital, Hamilton, Ont.
Rabinovitch, H. H., King's County Hospital, Brooklyn, N.Y.
Radford, C. J., Toronto Western Hospital, Toronto.
Richardson, D. A., Toronto General Hospital, Toronto.
Robertson, D. S., Toronto East General Hospital, Toronto.
Rodgerson, J. S., Toronto Western Hospital, Toronto.
Rosen, G. P., New Mount Sinai Hospital, Toronto.
Ross, M. B., New Mount Sinai Hospital, Toronto.
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Rudd, W. W. H., Toronto Western Hospital, Toronto.
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Scully, L. T., Vancouver General Hospital, Vancouver.
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Silver, J., Harrisburg Hospital, Harrisburg, Penna.
Simms, D. C., Hamilton General Hospital, Hamilton, Ont.
Skolnick, M., King's County Hospital, Brooklyn, N.Y.
Slatt, B., Toronto General Hospital, Toronto.
Smith, D. W. S., Toronto East General Hospital, Toronto.
Sohl, F., St. Charles Hospital, Toledo, Ohio.

Solursh, L. P., New Mount Sinai Hospital, Toronto.
Sorokolit, W. T., St. Michael's Hospital, Toronto.
Standen, J. R., Toronto Western Hospital, Toronto.
Steele, J. C., Toronto General Hospital, Toronto.
Stephen, D. H., Toronto East General Hospital, Toronto.
Stork, J., Toronto General Hospital, Toronto.
Sutherland, Mrs. L. R., Toronto General Hospital, Toronto.
Turchin, R., King's County Hospital, Brooklyn, N.Y.
Tuters, Miss L. M., St. Michael's Hospital, Toronto.
Van de Mark, T. B., Toronto Western Hospital, Toronto.
van Nostrand, A. W. P., Toronto Western Hospital, Toronto.
Warkentin, D. E., Toledo Hospital, Toledo, Ohio.
Warnica, J. K., Toronto General Hospital, Toronto.
Werry, E. C., Toronto General Hospital, Toronto.
White. L. W., Toronto General Hospital, Toronto.
Wilk, E. J., St. Joseph's Hospital, Toronto.
Williams, G. E., St. Joseph's Hospital, Toronto.
Wilson, D. R., Toronto General Hospital, Toronto.
Wintrob, R. M., King's County Hospital, Brooklyn, N.Y.
Wolstat, H., New Mount Sinai Hospital, Toronto.
Woodward, E. G., St. Joseph's Hospital, Toronto.
Woychuk, W., Toronto East General Hospital, Toronto.
Zajac, A. S., St. Michael's Hospital, Toronto.
Zimmerman, M. H., King's County Hospital, Brooklyn, N.Y.
Zuker, G. A., New Mount Sinai Hospital, Toronto, Ont.

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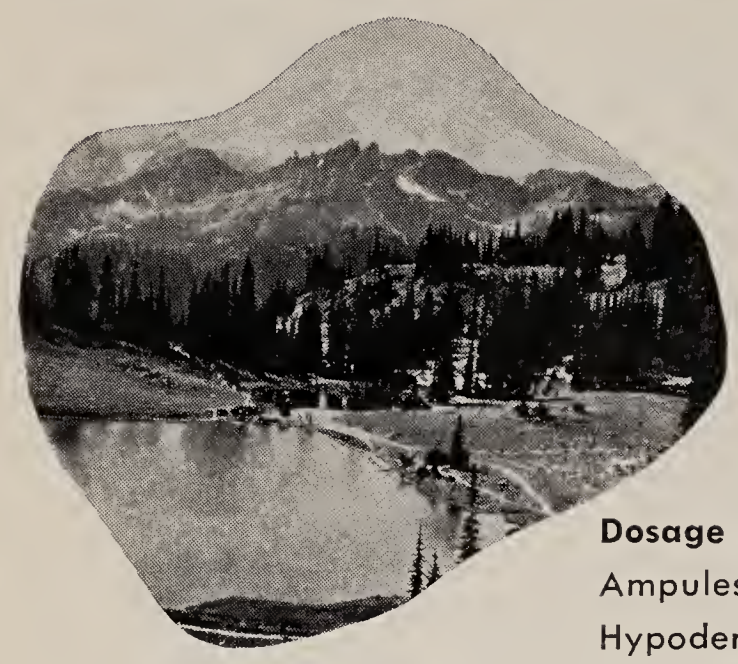

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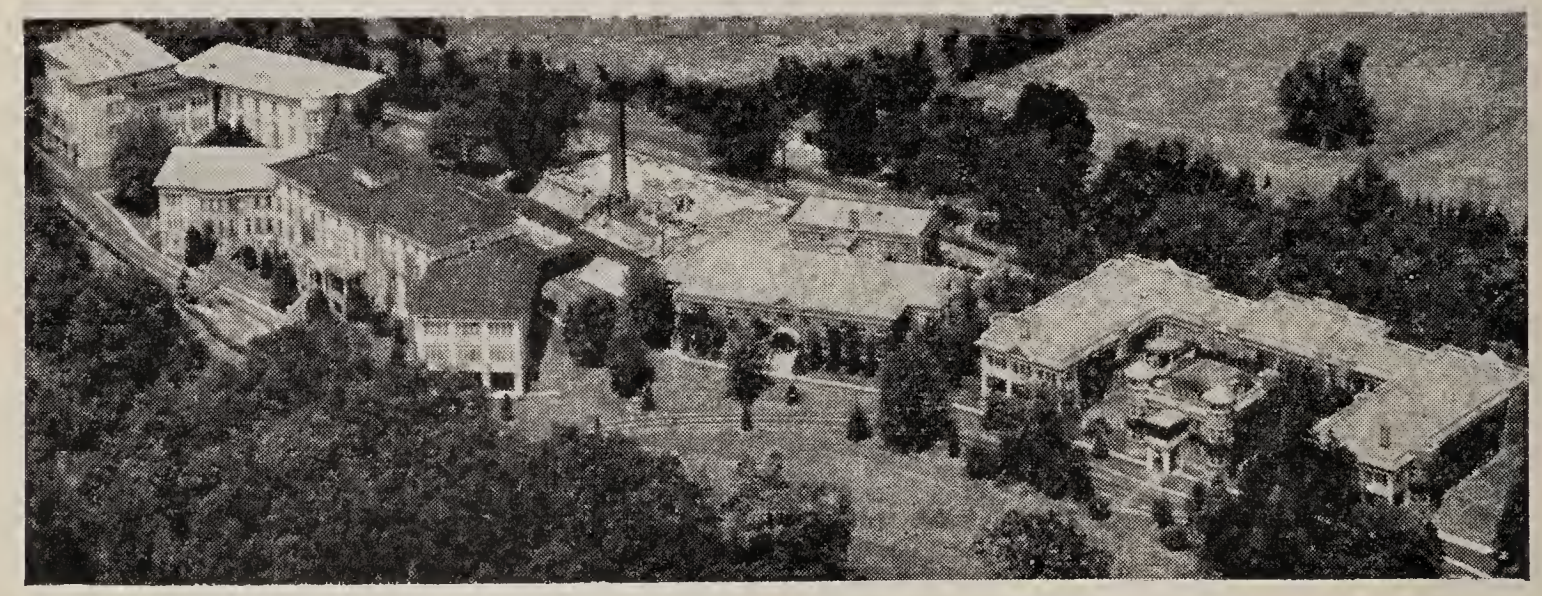

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1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.

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